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**The educational gradient in premature cardiovascular mortality; examining mediation by risk factors in cohorts born in the 1930s, 1940s and 1950s**

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## 1 ABSTRACT

2  
3 **Aims:** Educational inequality in cardiovascular disease (CVD) and in modifiable risk factors  
4 change over time and between birth cohorts. We aimed to assess how CVD risk factors  
5 mediate educational differences in premature CVD mortality and how this varies over birth  
6 cohorts and sex.

7 **Methods:** We followed 360,008 40-45 year olds born in the 1930s, 1940s or 1950s from  
8 Norwegian health examination surveys (1974-1997) for premature CVD mortality. Cox  
9 proportional hazard and Aalen's additive survival analyses provided hazard ratios and rate  
10 differences (RD) of excess deaths in participants with basic versus tertiary education.

11 **Results:** Relative educational differences in premature CVD mortality were stable, whereas  
12 absolute differences narrowed from the 1930s to the 1950s cohorts; RD per 100 000 person  
13 years declined from 170 (95% confidence interval 117, 224) to 49 (36, 61) in men and from  
14 60 (34, 85) to 23 (16, 29) in women. CVD risk factors attenuated RD's by 69% in both  
15 cohorts in men, and in women by 102% in 1930s and 61% in 1950s cohorts. Smoking had the  
16 single strongest influence on the educational differences for men in all three cohorts, and for  
17 women in the two most recent cohorts.

18 **Conclusion:** Smoking appeared to be the driving force behind educational differences in  
19 premature CVD mortality in the 1930s to 1950s birth cohorts for men and in the two recent  
20 birth cohorts for women. This suggests that strategies for smoking prevention and cessation  
21 might have the strongest impact for reducing educational inequality in premature CVD  
22 mortality.

23  
24 **Keywords:** Cardiovascular diseases, Mortality, Health behaviour, Educational status,  
25 Socioeconomic factors, Cohort effect

# 1 INTRODUCTION

2  
3 A substantial proportion of educational differences in cardiovascular disease (CVD) are  
4 mediated by CVD risk factors<sup>1-4</sup>. However, risk factors only contribute to educational  
5 inequality in disease if they are socially patterned, and this patterning may vary over time  
6 periods, cohorts and between sexes<sup>5-7</sup>. In Norway, surveys indicate that absolute educational  
7 inequalities in smoking have widened from the mid-1980s and up to 2008<sup>8, 9</sup>. In men, this was  
8 due to a faster decline in smoking rates among the highly educated, whereas in women  
9 smoking rates increased in the lower educational groups up to the millennium, in line with the  
10 smoking epidemic as described by Lopez<sup>8, 10</sup>.

11 Social patterning of CVD mortality has varied over time. Declining CVD mortality in  
12 Norway during the last four decades of the twentieth century was initially more rapid in the  
13 higher educated population yielding increasing absolute educational differences in CVD  
14 mortality up to year 2000 in men and up to 1980 in women<sup>11</sup>. This was followed by a  
15 subsequent narrowing, which was also found in other European countries<sup>11, 12</sup>. Studies from  
16 England and Scotland suggest evenly improved treatment uptake across all social groups<sup>13, 14</sup>.  
17 Changes in social patterning in both CVD risk factors and CVD mortality between birth  
18 cohorts and between sexes might be a key to understand changing trends in educational  
19 differences in CVD mortality. We are not aware of any study addressing differing impact of  
20 risk factors over birth cohorts and sex in cohorts followed over the same life course period.

21 We aimed to assess to what extent behavioural and biological modifiable CVD risk  
22 factors differ in their impact on the educational gradient in premature CVD mortality in  
23 cohorts born in the 1930s, 1940s and 1950s, examined at age 40-45; i.e. in the 1970s, 1980s  
24 and 1990s.

## **METHODS**

### **Study population**

From the Norwegian population based health examination surveys we selected health survey participants born in the 1930s, 1940s or 1950s, turning 40-45 years at the year of their health survey participation. Participants with the potential to reach age of 60 years during follow up were selected (Figure S1). The surveys included the Counties Studies (1974-88)<sup>15</sup>, the Age 40 Program (1985-1999)<sup>16</sup>, and the Cohort of Norway (CONOR) (1994-2003)<sup>17</sup> with overall participation rate of 86%, 70% and 58%, respectively.

Of 364,324 potential participants, we excluded 1.2% with missing risk factor levels and/or missing or no registered educational level, yielding a sample of 360,008 participants included in the analysis (Figure S1). In participants with missing risk factor values the proportion with basic education in the 1930s, 1940s and 1950s birth cohorts was higher (50%, 28% and 26%) than for those with valid values (48%, 24% and 18%).

### **Data linkage**

Based on the Norwegian Family Based Life Course Study<sup>18</sup>, data from health surveys were linked to national educational data, to the Norwegian Cause of Death Registry, and to the National Registry using the unique national personal identification number. If a participant attended several health surveys between ages 40-45 years, only the first survey was selected.

Permission to be absolved from professional secrecy and linking of data was granted by the Regional Ethics Committee South-East (in May 25<sup>th</sup> 2012, reference number 2012/872). The study complies with the Declaration of Helsinki.

## **Education**

A person's highest attained educational level was classified as either Basic (up to 7 years in the 1960s, up to 9 years from the 1970 and forth), representing compulsory primary and lower secondary school or lower levels, Secondary (10 - 12 years) representing completion of first, second or third year of upper secondary school, or Tertiary (13 years or longer) usually representing completion of a college or university degree. These categories correspond to the International Standard Classification of Education (ISCED) 1997 categories 0-2, 3-4 5-6.

## **Cardiovascular risk factors**

In all health examination surveys self-assessed questionnaires, clinical measures and non-fasting blood sampling were collected with similar methodology and questionnaires<sup>15-17</sup>.

Established CVD risk factors available for all birth cohorts were selected. Smoking status and cigarette pack years was collapsed into smoking grade: (1) never smoker, (2, 3) former smoker with < or  $\geq 20$  pack years, (4, 5) current daily smoker with < or  $\geq 20$  pack years.

Leisure time physical activity was harmonized into a four graded scale from sedentary (1) to hard physical (4). Self-reported treatment with antihypertensive medications and self-reported diabetes was recorded. Blood pressure was initially measured manually using sphygmomanometers and the second of two measurements defined systolic blood pressure.

Later, three automatic oscillometric measures were assessed and the average of the last two available measurements defined systolic blood pressure<sup>19</sup>. Height and weight were measured and body mass index (BMI) was calculated ( $\text{kg/m}^2$ ). Serum total cholesterol and triglycerides were initially measured by non-enzymatic, and later enzymatic method<sup>20</sup>.

## **Cardiovascular mortality**

Data on underlying cause of death from CVD was obtained from the Norwegian Cause of Death Registry through 2014 (ICD-8: 390-444.1, 444.3-458, 782.4, ICD-9: 390-459, ICD-10: I00-I99)<sup>21</sup>. CVD mortality before age 60 years was considered premature. The participants were followed prospectively from the time of health examination up to death, emigration or age 60 years.

## **Statistical methods**

Trend in risk factors across educational levels and across birth cohorts was tested. Premature CVD mortality rates per 100 000 person years were age-standardized using the study population as standard. Aalen additive hazard survival model (“timereg” package in R i.386 version 3.4) provided absolute estimates; rate differences (RD) in number of CVD deaths between basic versus tertiary, and basic versus secondary educational level per 100 000 person years with 95% confidence intervals<sup>22</sup>. Cox proportional hazards models (Stata version 14) provided relative estimates; hazard ratio (HR) with 95% confidence intervals. Analysis time was attained age in days. The following models examined risk of premature CVD mortality by education and mediation by risk factors: Educational level adjusted for year of birth (Model 1), educational level adjusted for year of birth and one of the following risk factors; smoking grade, systolic blood pressure and current antihypertensive medication, serum total cholesterol, serum triglycerides, BMI or physical activity (Model 1+ risk factor), and educational level adjusted for year of birth and all the studied risk factors (Model 1 + all risk factors). Validity of self-reported diabetes was considered limited and was included as risk factor in sensitivity analyses only; diabetes was not screened for like the other biological risk factors and did not distinguish between type 1 and type 2 diabetes in which educational gradients may go in opposite directions<sup>23</sup>.

Proportion of excess premature CVD deaths in basic versus secondary or tertiary educated that is mediated by risk factors (controlled indirect effect) was assessed as the difference in absolute mortality rates ( $\Delta RD$ ) between Model 1 (controlled total effect) and Model 1 + risk factor (controlled direct effect);  $RD_{\text{Model 1}} - RD_{\text{Model 1 + risk factor(s)}}$ . The mediated proportion was assessed by the ratio of the controlled indirect effect over the controlled total effect in percentage ( $\Delta RD$ , %);  $(RD_{\text{Model 1}} - RD_{\text{Model 1 + risk factor(s)}}) / (RD_{\text{Model 1}}) * 100$ . Year of birth and all risk factor variables were centred on the mean in the RD analyses. Bootstrapping with 1000 replications assessed the precision of the mediated proportion expressed as  $\Delta RD$  and  $\Delta RD$  in %.

Similar calculations assessing the relative excess mortality were performed using the  $\beta$ -coefficient (logarithm of hazard ratio (HR)) for education in Cox regression<sup>2</sup>;  $(\log HR_{\text{Model 1}} - \log HR_{\text{Model 1 + risk factor(s)}}) / (\log HR_{\text{Model 1}}) * 100$ .

None of the examined assumptions in Model 1 + all risk factors were violated: In Aalen's additive survival regression, plots of cumulative coefficients with simulated 95% confidence bands of each of the covariates on the outcome over time were inspected for constant or non-constant effect over time<sup>22</sup>. Proportional hazards assumptions were tested and Schoenfeld residuals inspected<sup>24</sup>.

Controlled effects assessed by adjustment for mediators provided estimates for mediation analyses, assuming no unmeasured confounding and no exposure-mediator interactions<sup>25</sup>. In case of the latter, natural total and indirect effects were calculated (Supplementary materials).

## RESULTS



1 The distribution of participants across educational groups changed markedly from the 1930s  
2 to the 1950s birth cohorts: the proportion with basic education decreased from 48% to 18%,  
3 and the proportion with tertiary education increased from 10% to 31%. This transition was  
4 similar for men and women (Table S1). The tertiary education groups had more favourable  
5 CVD risk factor profiles compared to those in the lower educational groups in men and  
6 women in all birth cohorts (Table S1).

7 The level of the CVD risk factors changed from the 1930s to the 1950s cohorts: Serum  
8 total cholesterol levels decreased, serum triglyceride levels increased, and the proportion of  
9 physically inactive had a net increase. The proportions of male current daily smokers  
10 declined, whereas female smoking increased in basic and secondary educated, and levelled off  
11 for tertiary educated. Systolic blood pressure levels increased in men with tertiary education,  
12 whereas the levels decreased in men with basic education and in the basic and secondary  
13 female educational groups. BMI levels increased for all male educational groups and for  
14 women with tertiary education, whereas women with basic education had a decrease in BMI  
15 levels (Table S1).

16 During the follow-up period of 6,488,891 person years (mean 18 years; range 1 day to  
17 21 years), in all 16,665 persons died prematurely from any causes (4.6 % of the study  
18 population), 3,871 persons died prematurely from CVD (1.1 %), and 0.5 % emigrated.  
19 Premature CVD mortality was lower in women compared to men and declined for both sexes  
20 by more recent birth cohorts (Table S2).

21 In analyses of absolute educational differences adjusted for year of birth, the rates of  
22 excess premature CVD deaths in basic versus tertiary educated (RDs) decreased by more  
23 recent birth cohorts (Table 1, Figure S2). The relative differences, i.e excess premature CVD  
24 mortality in basic relative to tertiary educated expressed as HRs, were more or less stable over  
25 the three birth cohorts from the 1930s, 1940s and 1950s (Table S3). About two thirds of the

1 excess premature CVD deaths in the basic versus the tertiary educated were due to their  
2 unfavourable risk factors for all birth cohort groups, except women in the 1930s cohort, where  
3 all of the excess CVD mortality in those with basic education were mediated through the CVD  
4 risk factors (Table 1, Figure S2).

5 Adjustment for each isolated risk factor indicated that smoking mediated nearly one  
6 third or more of the excess premature CVD deaths in the basic versus the tertiary educated in  
7 all the birth cohort groups for both sexes. Of all CVD risk factors, smoking grade seemed the  
8 single strongest mediator, except in women from the 1930s cohort. Here, systolic blood  
9 pressure, smoking grade and serum total cholesterol, each seemed to mediate about one third  
10 or one fourth of the excess CVD mortality in those with basic education.

11 From the 1930s to the 1950s cohorts, the influence of systolic blood pressure on the  
12 difference in CVD mortality between basic and tertiary educated was reduced by one half for  
13 both sexes. This was also the case for serum total cholesterol in women and for physical  
14 activity for men, whereas the influence of serum total cholesterol in men and physical activity  
15 in women were stable from the 1930 to the 1950s cohorts. The influence of BMI and serum  
16 triglycerides on the excess CVD mortality on the basic educated was not significant in any of  
17 the cohorts (Table 1).

18 Highly significant interactions (by  $p < 0.001$ ) between education and CVD risk factors  
19 were only observed in the additive analyses. Educational level interacted with serum total  
20 cholesterol levels in women born in the 1940s, and with smoking grade in men born in the  
21 1940s. For these two settings, natural total and indirect effect estimates were similar to the  
22 controlled effects presented in Table 1 (Table S4). Self-reported diabetes (prevalence 0.7%)  
23 mediated a minimal proportion of excess premature CVD mortality by lower education  
24 (Tables S5-S7).

1           The proportion who died prematurely from CVD in the 1930s, 1940s and 1950s  
2 cohorts was higher among participants excluded because of missing data for education (4.0%,  
3 3.9% and 2.6%) or CVD risk factors (3.1%, 2.5% and 1.9%) than among included participants  
4 (2.6%, 1.2% and 0.7% (Figure S1)), respectively.

## 6 **DISCUSSION**

7 Excess absolute number premature CVD deaths per 100 000 person years in the basic versus  
8 the tertiary educated group declined in more recent birth cohorts, whereas relative educational  
9 differences were stable over cohorts. Over two thirds of this gap in premature CVD deaths  
10 between basic and tertiary educated was mediated by the modifiable CVD-risk factors  
11 smoking, systolic blood pressure, total cholesterol, BMI, triglycerides and physical activity.  
12 The strength of mediation was similar across genders and birth cohorts, except from the oldest  
13 birth cohort in women where the CVD-risk factors fully mediated the excess premature CVD  
14 deaths in the basic educated. Smoking seemed to be the single strongest mediator in all three  
15 birth cohorts for men, and in the two most recent birth cohorts for women.

17 The major strengths are that our study is population-based, includes a considerable number of  
18 participants examined at the same age born within three decades. Our study has assessed both  
19 biologically measured and behavioral risk factors, and includes absolute, relative and sex-  
20 specific analyses. Mediation by risk factors may have been stronger if more CVD risk factors  
21 than those available for all birth cohort had been included, such as diet, alcohol consumption,  
22 objective assessment of physical activity or use of cholesterol lowering medication.

23           To our knowledge only one other study has examined the difference in magnitude of  
24 mediation by risk factors on social inequality in disease over birth cohorts<sup>26</sup>. This population-  
25 based cohort from West Scotland compared the magnitude of mediation in two birth cohorts

1 with 20 years age-difference examined during the same calendar time. Here, the effect of  
2 behavioral risk factors on the occupational gradient in all-cause mortality was numerically  
3 stronger for a cohort born in 1952 than for a cohort born in 1932 examined and followed for  
4 the same calendar time period. These results were not comparable to our study since we have  
5 examined changes over different calendar periods at fixed point in the life course, at age 40-  
6 45 years.

7 Our study strongly suggest that smoking is of particular importance in Norway as a  
8 modifiable source of educational differences in CVD mortality. European countries have  
9 reported similar or weaker impact of smoking on inequality in health: In comparable French  
10 and British birth cohorts smoking accounted for 4% and 30%, respectively, of the  
11 occupational gradient in all-cause mortality<sup>4</sup>, and in a Dutch cohort smoking accounted for  
12 28% of educational gradient in incident coronary heart disease<sup>27</sup>. Interestingly, in our cohorts  
13 BMI followed a similar but inverse pattern as for smoking habits: By more recent birth cohort  
14 mean BMI levels increased in men along with decreasing levels of smoking. In women BMI  
15 decreased slightly in basic and secondary educated along with increasing smoking prevalence,  
16 and leveled off both for smoking prevalence and BMI development in the tertiary educated.

17 The composite mediating effect of risk factors over birth cohorts has a striking  
18 stability for absolute and relative excess premature CVD mortality by lower education, and  
19 with smoking as the major mediator. The exception is for women born in the 1930s where all  
20 of the excess deaths in the basic educated were due to their unfavorable risk factors, and  
21 where blood pressure seems to be of importance. Women with tertiary education seemed to  
22 follow the same pattern of change in risk factors by more recent birth cohort, as men. One  
23 might speculate that men with tertiary education being at the latest phase of the smoking  
24 epidemic, would be the first educational group to experience any new developments in risk  
25 factors over time. The increase in mean blood pressure by more recent birth cohorts in tertiary

1 educated men is somewhat alarming, still, this could be explained by the educational shift  
2 with a higher proportion having higher education in the more recent birth cohorts.

3 In conclusion, known CVD risk factors have a strong impact on absolute and relative  
4 excess premature CVD mortality by lower educational level in the 1930s, 1940s and 1950s  
5 birth cohorts. In men smoking was the driving force behind educational differences from the  
6 1930s birth cohorts and forth. In women smoking became the single most important CVD risk  
7 factor for educational differences from the 1940s birth cohorts, one decade later than in men.  
8 In Norway and other countries at a late stage of the smoking epidemic, strategies for smoking  
9 cessation and prevention of smoking initiation might have the strongest impact for reducing  
10 educational inequality in premature CVD mortality.

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4

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7

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9

10   *Availability of data:* The approval from the Ethics Committee does not include permission to  
11   make data materials available. IA had full access to all the data in the study and takes  
12   responsibility for its integrity and the data analysis.

13

14   **Authorship:** ON, BHS and OAS contributed to the conception or design of the work. IA,  
15   BHS, MKRK, OAS. LHM, HS, SGI and ON contributed to the acquisition, analysis, or  
16   interpretation of data for the work. IA drafted the manuscript. IA, BHS, MKRK, OAS. LHM,  
17   HS, SGI and ON critically revised the manuscript. All gave final approval and agree to be  
18   accountable for all aspects of work ensuring integrity and accuracy

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